UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,063	06/01/2001	Yuk-Ming Dennis Lo	JAK-PT001.1	3772

3624 7590 11/16/2001

VOLPE AND KOENIG, P.C.
SUITE 400, ONE PENN CENTER
1617 JOHN F. KENNEDY BOULEVARD
PHILADELPHIA, PA 19103

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1655	2

DATE MAILED: 11/16/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/872,063	Applicant(s) LO ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. This application is a continuation of 09/380,696, filed November 29, 1999 and a 371 of GB98/00690, filed March 4, 1998. This application also claims priority to GB9704444, filed March 4, 1997.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample, does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to us the invention commensurate in scope with these claims.

The claims are broadly drawn to a detection method performed on serum or plasma of a pregnant woman to detect any fetal DNA at any point in pregnancy.

The specification teaches fetal DNA has been detected in both serum and plasma. Table 2 and 3 show the quantification of fetal DNA in maternal serum and plasma in relation to the gestational age (pg. 33). The specifications teaches the detection of the Y-chromosome by markers to DYS14 locus and SRY gene. The specification teaches that plasma and serum samples were collected from 43 pregnant women with gestational ages from 12 to 40 weeks (pg. 9, para. 1). Of the 30 male fetuses, detection of a Y-positive signal occurred in 24 plasma samples and only 21 serum samples (pg. 9,para. 1). The specification also teaches a RhD status determination from plasma of RhD-negative pregnant women (pg. 15 and Table 1, pg. 20). The specification teaches that the DNA detected is paternally inherited (page 4, para 18) and requires amplification.

The art teaches unpredictability in detecting fetal DNA in plasma before the 15th week of gestation, of detecting paternally inherited non-Y sequences, and the unpredictability of detecting fetal DNA in serum samples. Specifically, Lo et al (New England J. of Med. , Vol. 339, No. 24, pages 1734-8, December 1998) teaches reliable results for fetal RhD status determination were obtainable from the 15th week of gestation and beyond in RhD negative women. Lo teaches that 7 of 9 fetus were positive on PCR testing for RhD genotyping (Table 1, pg. 1736). Lo teaches that two women with gestation ages of eight and nine weeks yielded false negative results (pg. 1735, col. 2, para. 6). Lo explicitly states "our data suggests that results of the RhD PCR test are reliable beginning in the second trimester" (pg. 1736, col. 2, para. 2). Additionally, Lo (Annals of Medicine, Vol. 31, NO. 5, pg. 308-312, Oct 1999) teaches "it

is likely that future improvements in technology may allow more accurate diagnosis to be made and potentially extend the applicability of this method to the first trimester of pregnancy" (pg. 310, col. 2, para. 1) suggesting that the technology does not currently exist and may not have been conceived of as of yet what would be required to diagnose in the first trimester.

Moreover, the art teaches the detection of fetal DNA in maternal plasma for an expanded CGT trinucleotide repeats, in the DM kinase gene on chromosome 19, in the range of 50-4000 repeats (Amicucci et al, February 2000, Clinical Chemistry, Vol. 46, No. 2, pages 301-302). Amicucci teaches sampling of plasma from pregnant women at 10 weeks of gestation to detect the expanded repeat present only in the father. Amicucci states "at present, this test seems appropriate only for monitoring paternally inherited expanded alleles" (pg. 302, para. 2). Additionally, Lo (Annals of Medicine, Vol. 31, NO. 5, pg. 308-312, Oct 1999) states "the success of the detection of fetal-derived RhD gene in the plasma and serum of pregnant women opens up the possibility that a similar approach may be used for other single-gene disorders" (pg. 310, col. 2, para. 3). However, Lo has not taught single gene disorders other than RhD which may in fact use this technique. Furthermore, the RhD analysis was only shown to be successful on RhD-negative women. The language of the paper is that of suggestion, and hypothesis rather than of evidence that this method works for these suggested single-gene disorders.

The art provides a summary of the state of the art (Pertl et al. Obstet Gynecol, Vol. 98, No. 3, pages 483-90, September 2001). Pertl et al (herein referred to as Pertl)

teaches that a search was conducted of the art from 1970-2000 and provides a summary of the state of the art. Pertl teaches that the "diagnostic use of circulating fetal DNA in maternal plasma is currently limited to genes that are present in the fetus but not in the mother". Further, discussion of the effectiveness of the analysis beginning in the second trimester is provided. Pertl suggests that "the main limitation at present appears to be the availability of uniquely fetal gene sequences that will identify the presence of fetal DNA in both male and female fetuses" (page 484). Pertl teaches that fetal DNA has been detected by PCR amplification and a real-time quantitative PCR assay. Pertl also discusses the detection of fetal aneupoidy, such that "this method can be applied only to a very small number of paternally inherited fetal aneuploidies. Furthermore, the selected markers must be informative, with both paternal alleles sizes differing from those of the mother." (page 487, col. 2).

Neither the specification nor the art provides guidance to overcome the unpredictability of detecting fetal DNA in plasma before the 15th week of gestation, of detecting non-paternally inherited sequences. It would require undue experimentation for the ordinary artisan to practice the invention as broadly as claimed. The concentration of fetal DNA in maternal plasma at early stages of gestation appears to be low. Thus predictably detecting fetal DNA in maternal plasma samples before the 15th week of gestation is unpredictable and would require the ordinary artisan to enrich the fetal DNA in some manner which have not been described such as PCR amplification. The specification does not provide any information as to the quantity of fetal nucleic acids present during the first trimester of pregnancy. It is highly

unpredictable as to whether sufficient quantities of fetal nucleic acids are present in maternal serum or plasma during the first trimester of pregnancy as to allows for the specific detection of fetal nucleic acids. It is unpredictable that the fetal nucleic acids could be detected without first amplifying the fetal nucleic acids.

The detection of a maternally inherited nucleic acid from the fetus is unpredictable. The specification explicitly states that "the method of the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother" (pg. 4, lines 5-7). As stated in numerous of the papers the concentrations of fetal DNA in maternal plasma may reach 3.4% in early pregnancy and 6.2% in late pregnancy, however, there is a much higher percentage of maternal DNA in the plasma. Provided that the skilled artisan obtained a positive result for detection of the nucleic acid, it would require undue experimentation determine whether the nucleic acid was a results of the maternal DNA found in the maternal plasma or whether in fact the nucleic acid was from the fetus. The specification does not provide any teachings nucleic acids which are specific to the fetus and absent in the maternal serum/plasma. Thus, detection of a maternally inherited nucleic acid would be unpredictable and require undue experimentation.

With respect to claim 5, applicant has not provided that one would be able to, without unpredictability, detect fetal nucleic acid by merely taking a sample of serum or plasma with a sequence specific probe. Applicant has illustrated the need for amplification or purification. The background within serum and plasma of maternal DNA in addition to other elements would be very high.

With respect to Claim 12, applicant has not provided any guidance to the skilled artisan to practice the claim without unpredictability. The specification describes detection of RhD and Y chromosome. The specification does not provided detection of a disease phenotype. It is unpredictable that a disease phenotype which occurs due to a single point mutation would be detectable.

With respect to claims 27, 29-32, the claims are drawn to maternal or fetal conditions or characteristics. However, this term is extremely broad. The specification has only described and enabled the prenatal diagnosis of sex, RhD and pre-eclampsia which does not provide enablement for any condition or characteristic. This encompasses, determining hair color, left-handedness, weight status, all of which are conditions and characteristics which are not enabled.

With respect to Claim 31, the claim is broadly drawn to a method of prenatal diagnosis for a condition which comprises obtaining a serum/plasma sample and determine the presence or absence of one or more selected nucleic acid sequence in the detected fetal nucleic acid. The absence of a sequence it not supported. As stated above, it is unpredictable without amplification or enrichment that the lack of detection is indicative of the lack of the presence. Further, applicants have only illustrated paternally inherited nucleic acids.

Thus, the above analysis demonstrates that the skilled artisan would be required to perform undue experimentation to make and use the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 5-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 5-16, 22-32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: amplification of the nucleic acids. With out the amplification step, there appears to be a gap between the sample and the detection step.

B) Claim 14 is indefinite because, the claim depends upon claim 9 which is for Rhesus D genotyping in a RhD mother. However, Claim 9 is not drawn to RhD. It appears that the claim lacks proper antecedent basis and may have been intended to depend from Claim 13.

C) Claims 16-21 are indefinite because, The claims are drawn to determining the concentration, however, Claim 6 which the claim depends is drawn to the X chromosome sequence. It appears that the claim may have been intended to depend from Claim 1. As the claim is written, the claim does not make sense.

D) Claim 19 is indefinite over the recitation of "normal". It is unclear what constitutes "normal". Normal is a relative term which has not been described in the specification.

E) The term "substantially all" in claim 27 is a relative term which renders the claim indefinite. The term "substantially all" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

F) Claim 27, 29-32 are indefinite because it is unclear the meaning of maternal or fetal condition or characteristics. This phrase is not defined in the specification and it is unclear as to what is intended to be encompassed by maternal conditions and characteristics.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,258,540, July 10, 2001. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application are drawn to methods of detecting fetal DNA in a sample from maternal serum or plasma. The

claims of patent 6,258,540 are drawn to methods of detecting paternally inherited DNA of fetal origin by amplifying the paternally inherited nucleic acid from plasma or serum and detecting the presence of the fetal DNA.

5. Claims 1-32 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 09/876,005. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of 09/876,005 are directed to methods for prenatal monitoring on a blood sample which does not contain anucleated cells and testing the sample for fatal RNA. While the claims of 09/876,005 are drawn to method which detect RNA, RNA is clearly within the genus of fetal nucleic acids. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

6. No Claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
November 7, 2001

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600